

What is claimed is:

1. A method for the hierarchical classification of unknown cell-specific proteins by listing known body organs, tissues, and locus-specific cell types, as manifesting cell-specific proteins.
2. A method of claim 1 where the said hierarchical classification is a basis for a number system, whereby said cell-specific proteins of any cell type are indirectly assigned a number.
3. A method for identifying constitutively expressed locus-specific proteins in the brain, the deactivation of which selectively impairs the otherwise normal behavioral response to a particular stimulus, comprising of:

first means for measuring the minimal change in said stimulus, of constant intensity and duration, and within the same sensory submodality, that elicits said behavioral response, whereby said behavioral responses to said stimuli correlate with subjective states;

second means for identifying brain loci, the deactivation of which selectively impairs said behavioral response to said stimuli, whereby said brain loci is correlated with said behavioral responses to said stimuli and whereby said brain loci is correlated with said subjective states;

third means for identifying said proteins specific to said brain loci, the deactivation of which selectively impairs said behavioral response to said stimuli, whereby said behavioral responses to said stimuli are selectively impaired, thereby whereby function of said proteins correlate with said behavioral responses and whereby function of said proteins correlate with said subjective states.

4. A method of Claim 3 for the selective amplification of mRNA transcription by using subjecting model mammalian animals to persistent specific stimulus of fixed duration and intensity.
5. A method of Claim 4 where the said model animals are in their postnatal critical stage.

Downloaded from att.net

## V. A chronological note

In 1970, while a student at City University of New York, I outlined in a paper on the mind/brain problem why sensations are innate and determined by the local anatomic specificity of brain loci evoking them. About that time I formed Q1 Corporation, a company that developed the first 8-bit microcomputer system, which was delivered to Litton Industries in December 1972. The system utilized the 8008 microprocessor -- the first member of Intel's Pentium microprocessor family. A subsequent version of the system, based on the 8080, was then installed in the eleven bases of the National Aeronautics and Space Administration (NASA). In 1980 I resigned my position as president of Q1 and returned to the study of the mind/brain problem.

The basic problems that needed resolution were epistemological rather than technical. Until recently, most scientists shied away from the subject, while the contribution of philosophers to the field was negative. Consequently, addressing and resolving these issues turned out to be a virtually solitary undertaking. In 1995 an updated version of my 1970 paper was published by *Synthese*. In 1997 I discussed with Nadya Bobko, a biochemist at City University, the conceptual framework and how it provides a conceptual solution to the problem of muscle and bone loss in extended weightlessness. In 1998 I sent a letter to NASA suggesting that they pursue this proposed conceptual solution. That year I also sent, through Dr. James Watson, a draft of the identification method to Dr. Francis Crick, but was informed that he does not accept papers unless they were published in refereed journals. In 2000 I had a series meeting with Benjamin Bartelle, a biochemist at Cold Spring Harbor Laboratories. I presented to him the conceptual framework and the identification methods. He then accepted my suggestion to shift focus to the molecular neurobiology of elementary mental states, and begin by identifying the molecular correlates of the eight types of direction orientation columns visual area V5.

## W. Appendix A. A review of five indirectly related basic issues

1. *General, non-specific consciousness and attention.* Elementary mental states, perception, and cognition, may be viewed as foreground events against general, non-specific background consciousness (Chalmers 2001). Background consciousness, like ambient light, has gradations from mania to depression, sleep, anesthesia, and coma. In addition, there are mechanisms that serially shift the focus attention, and heightened conscious activity, among brain loci. Background consciousness and attention are necessary for awareness of foreground events, which some call the specific *contents* of consciousness. In contrast, a foreground event, like tasting sweet or seeing red can be selectively inactivated. Background consciousness is innate, is evoked in the CNS, and has no more basic constituents. It therefore satisfies the criterion of an elementary mental state. Satisfying the conjunction of the conditions for background consciousness, attention, and foreground mental state constitute the sufficient condition for consciousness.
2. *Sensory awareness without activation of the anterior association cortex.* The conceptual framework implies that sensations are evoked in secondary sensory cortical areas. Some neuroscientists have assumed that the anterior association cortex must also be activated for these mental states to be experienced. Recent experiments, however, have demonstrated that this is not the case. During rapid eye movement (REM) dreams, for example, the limbic system and secondary sensory cortical areas are activated, but the anterior association cortex is not. Moreover, the primary sensory cortical areas also remain inactive (Braun et al. 1998).
3. *Ultimately, all observation is made from the first-person perspective.* Observations of a person may be partitioned into those that are consistent with observations of others, and those that are not. Both types of observations are private, and thus subjective. The intersubjectively consistent observations are called “objective,” the other, “subjective.” Thus, first-person perspective underlies, and has epistemological priority over, third-person perspective.

4. *The mind is not an emergent property of brain function.* Physicalism inverts the epistemological priority of the first- and third-person perspectives. This inversion leads to the conclusion that mental events are an emergent property of brain function. For example, some scientists, who recognize that color is evoked in the brain, have been led to conclude that it does not exist outside the brain (Martin 1991), and that the world was colorless for billions of years until brains evolved (Stapp 1993). The mind is not an emergent property of brain function, and it cannot be “reduced” to the physical. The identification of physical correlates of mental states is a preliminary stage towards formulation of the findings in terms of first-person perspective.
  
5. *Teleology and feedback mechanisms in the cell, body, and brain.*
  - 5.1 Homeostatic maintenance of thermodynamic disequilibrium in the cell. Rosenblueth, Wiener, and Bieglow (1943) have shown that explaining biological and artificial systems in teleological, goal-oriented, or feedback mechanisms is consistent with physics. Teleological explanations are not only legitimate but also necessary. Life of a cell is often characterized in terms of it being far from thermodynamic equilibrium. But so is a rock on a mountaintop. However, only the cell, while it is alive, has negative and positive feedback mechanisms (stabilization and amplification respectively) to maintain, and within limits restore, this *disequilibrium*. Consider the membrane potential of a living cell. The inside is electrically negative relative to the outside. *The cell maintains this imbalance in a steady state* (called “the resting potential”) by actively transporting ions against their gradients. After disruption of the membrane potential in the neuron, it is restored within about a millisecond.
  
  - 5.2 Teleological mechanisms and brain function. Some teleological mechanisms, such as the immune system, are specific to multicellular organisms, underscoring the fact that health and disease are intrinsically normative. Teleological mechanisms are central to accounting for brain function. One of the set-points homeostatically maintained by the hypothalamus, for example, is the glucose level in the blood. This regulation is not conscious when automatic, but evokes hunger when voluntary action is needed. Similarly, thermoregulation in mammals is not conscious while temperature homeostasis can be maintained automatically, but the mental state of being cold is

evoked when a voluntary action is called for. The teleologic aspects of pleasure and pain, for example, are self-evident.

## X. References

- Aatinski, JT. Coupled one-step reverse transcription and polymerase chain reaction procedure for cloning large cDNA fragments. *Methods in molecular biology*. BA White (ed.). 1997.
- Abel, T, KC Martin, D Bartsch, and ER Kandel. Memory suppressor genes: Inhibitory constraints on the storage of long-term memory. *Science*. 1998. 279: 338-341.
- Adelman, LM. Molecular computation of solutions to combinatorial problems. *Science*. 1994. 266: 1021-1024.
- Agrawal, S and Q Zhao. Antisense therapeutics. *Current opinion in chemical biology*. 1998. 2: 519-528.
- Albright, T. Direction and orientation selectivity of neurons in visual area MT of the macaque. *J of Neurophysiology*. 1984. 52: 1106-1130.
- Anderson, WF. Gene therapy. *Nature*. 1998. 395: 25-30.
- Basebaum, AJ and TM Jessell. The perception of pain. In *Principles of Neural Science*. 4<sup>th</sup> edition. Edited by ER Kandel et al. New York: McGraw-Hill. 2000.
- Beckers, G and S Zeki. The consequences of inactivating areas V1 and V5 on visual perception. *Brain*. 1995. 118: 49-60.
- Bethke, BD, and B Sauer. Rapid generation of isogenic mammalian cell line expressing recombinant transgenes by use of Cre Recombinase. *Methods in molecular biology*. E Kmiec (ed.). Totowa, NJ: Humana Press. 2000.
- Borsook, D, (ed.). *Molecular neurobiology of pain*. Seattle, Wash. IASP Press. 1997.
- Braun, AR, et al. Dissociated pattern of activity in visual cortices and their projections during human rapid eye movement sleep. *Science*. 1998. 279: 91-95.
- Britten, KH, MN Shalden, WT Newsome and JA Movshon. The analysis of visual motion: a comparison of neuronal psychophysical performance. *J neuroscience*. 1992. 4745-4761.
- Brodmann, K. *Vergleichende lokalisationslehre der grosshirnhinde*. Leipzig: Barth. 1909.
- Buck, LB. Smell and taste: the chemical senses. In *Principles of Neural Science*. 4<sup>th</sup> edition. Edited by ER Kandel et al. New York: McGraw-Hill. 2000.
- Buck, LB. and R Axel. A novel multigene family may encode odorant receptors. *Cell*. 1991. 65: 175-187.

- Burcin, MM, et al. Adenovirus-mediated regulable target gene expression *in vivo*. *PNAS, USA*. 1999. 96: 355-360.
- Buxhoevedn, DP, et al. Quantitative analysis of cell columns in the cerebral cortex. *J. of neuroscience methods*. 2000. 97: 7-17.
- C. *Elegans* Sequencing Consortium. Genome sequence of the nematode *C. Elegans*: A platform for investigation biology. *Science*. 1998. 282: 2017-18.
- Cahill, L, and J McGaugh. Mechanism of emotional arousal and lasting declarative memory. *TINS*. 1998. 21: 294-299.
- Celis, JE, et al. Human and mouse proteomic databases: Novel resources in the protein universe. *FEBS. Lett*. 1998. 430: 64-72.
- Chalmers, DJ. What is a neural correlate of consciousness? In *Neural correlates of consciousness: Empirical and conceptual questions*. Edited by T Metzinger. 2000. Cambridge, Mass. The MIT Press.
- Chee, M, R Yang, E Hubbell, A Berno, XC huang, D Stern, J Winkler, DJ Lockhart, MS Morris and SPA Fodor. Accessing genetic information with high-density DNA arrays. *Science*. 1996. 274: 610-614.
- Cinelli, AR. High-definition mapping of neuronal activity using voltage-sensitive dyes. *Methods*. 2000. 21: 349-372.
- Davidson, B. et al. A model system for *in vivo* gene transfer into the central nervous system using adenoviral vector. *Nature Genetics*. 1993. 3: 219-23.
- Dehaene, Stanislas. *The number sense: How the mind creates mathematics*. 1997. Oxford: Oxford University press.
- Demeneix, BA., M Ghorbel, and D Goula. Optimizing polyethylenimine-based gene transfer into mammalian brain for analysis of promoter regulation and protein function. *Gene targeting protocols*. E Kmiec (ed.). Totowa, NJ: Humana Press, Inc. 2000.
- Dobelle, W, et al. A prostheses for the deaf based on cortical stimulation. *Ann Otol*. 1973. 82: 445-463.
- Dobelle, W, et al. Artificial vision for the blind: Electrical stimulation of the visual cortex offers hope for a functional prostheses. 1974. *Science*. 183: 440-444.
- Doering, LC. Components of cell and gene therapy for neurological disorders. *Molecular medicine and gene therapy*. Edited by TF Krestina. 2001. New York: Wiley-Liss
- Favorov, O. and BL Whitsel. Spatial organization of the peripheral input to area 1 cell columns. I. The detection of "segregates". *Brain res rev*. 1988. 472: 25-42.
- Finger, S. *Origins of neuroscience*. Oxford. Oxford University Press. 1994.
- Finegold, AA, et al. A paracrine paradigm for *in vivo* gene therapy in the central nervous system: treatment of chronic pain. *Human gene therapy*. 1999. 10:1251-1257.
- Fujita, I, K Tanaka, M Ito and K Cheng. Columns for visual features of objects in monkey inferotemporal cortex. *Nature*. 1992. 360: 343-346.
- Garber, K. An end to Alzheimer's? *Technology Review*. March 2001.

- Gershorn, ES, JA Bander, et al. Closing in on the genes for manic-depressive illness and schizophrenia. *Neuropharmacology*. 1998. 18: 233-42.
- Gilbertson, TA, S Damak and RF Margolskee. The molecular physiology of taste transduction. *Current opinion in neurobiology*. 2000. 10: 519-527.
- Hadjikhani, N, AK Liu, AM Dale, P Cavanagh, RBH and Tootell. Retinocopy and color sensitivity in human visual cortical area V8. *Nature neuroscience*. 1998. 3: 235-241.
- Hebb, DO. *The organization of behavior*. New York: Wiley. 1949.
- Held, R. Perception and its neuronal mechanisms. *Neurobiology of cognition*. PD Eimas and AM. Galaburda (eds.). The MIT Press. 1994.
- Hering, E. *Outline of a theory of the light sense*. Trans. by Hurvich and Jameson. Cambridge: Harvard University Press. 1920/1964.
- Hermann, T. and DJ Patel. Biochemistry-adaptive recognition by nucleic acid aptamers. *Science*. 2000. 287: 820-825.
- Jameson, D. and LM Hurvich. Essay concerning color vision. *Annual Review of Psychology*. 1989. 40: 1-32.
- Jerne, NK. Antibodies and learning: selection versus instruction. In *The neurosciences: A study program*. Quatron, G, T Melneckuck and FO Schmitt (eds). New York: Rockefeller University Press. 1967.
- Kay, BJ, Winter, and J McCafferty. *Phage display of peptides and proteins: A laboratory manual*. London: Academic Press. 1996.
- Kelly, JP. Hearing. In *Principles of neural science*. 3<sup>rd</sup> edition. Edited by ER Kandel et al. New York: Elsevier Science Publishing. 1991.
- Klose, J. Fractionated extraction of total tissue protein from mouse and human for 2-D electrophoresis. *Methods Mol. Biol.* 1999. 112: 147-172.
- Klose, J. Large-gel 2D electrophoresis. 1999. *Methods of Mol. Biol.* 112: 147-172.
- Kmieć, EB. Gene therapy. *Am. Scientist*. 1999. 87: 240-47.
- Kohl, S et al. Total colorblindness is caused by mutations in the gene encoding for the  $\alpha$ -subunit of the cone photoreceptor cGMP-gated cation channel. *Nature genetics*. 1998. 19: 257-259.
- Link, AJ, et al. Direct analysis of protein complexes using mass spectroscopy. *Nature Biotechnol.* 1999. 17: 676-682.
- Locke, John. *An essay concerning human understanding*. Edited with an introduction by PH Niddith. Oxford: Clarendon Press. 1705/1975.
- MacBeath and SL Schreiber. Printing proteins as microarrays for high-throughput function determination. *Science*. 2000. 289: 1760-1763.
- Maulik, S, and S Patel. *Molecular biotechnology*. New York: Wily-Liss. 1997.
- Martin, JH. Coding and processing of sensory information. In *Principles of neural science*. 3<sup>rd</sup> ed. Edited by ER Kandel et al. New York: Elsevier. 1991.
- McCulloch, WS and WH Pitts. A Logical calculus of the ideas immanent in nervous activity. In *Embodiments of mind*. W. S. McCulloch. The MIT Press. 1943/1970.
- Melzak, R. Phantom limbs and the concept of the neuromatrix. *TINS*. 1990, 13: 88-92.



- Miyamoto, RT, MJ Osberger, AM Robbins, WA Nyers, & Kessler. Prelingually deafened children's performance with the nucleus multi-channel cochlear implant. *The American Journal of Otology*. 1993. 14: 437-445.
- Mountcastle, VB. The columnar organization of the neocortex. *Brain*. 1997: 120: 701-22.
- Nabel, GJ. Development of optimized vectors for gene therapy. *PNAS USA*. 1999. 96: 324-326.
- Nathans, J, TD Hogness, DS. Molecular genetics of human color vision: the genes encoding blue, green, and red pigments. *Science*. 1986. 232: 193-202.
- Newsome, WT. Perceptual processes. In *Conversations in the Cognitive Neurosciences*. Edited by MS Gazzaniga. Cambridge, Ma. The MIT Pres. 1997.
- Newsome, WT, and EB Pare. A selective impairment of motion perception following lesions of the middle temporal visual area (MT). *J. Neuroscience*. 1988. 8: 2201-2211.
- O'Leary, DDM, et al. Molecular development of sensory maps: Representing sights and smells in the brain. *Cell*. 1999. 96: 255-269.
- Paulus, W, et al. Differential inhibition of chromatic and achromatic perception by transcranial magnetic stimulation of the human visual cortex. *NeuroReport*. 1999. 10: 1245-1248.
- Penfield, W, and T Rassmussen. *The cerebral cortex of man: A clinical study of localization of function*. New York: Macmillan. 1950.
- Pennington, SR, and MJ Dunn, Editors. *Proteomics: From protein sequence to function*. 2001. New York: Springer-Verlag.
- Recanzone, G, C Schneider and M Merzenich. Plasticity in the frequency representation of primary auditory cortex following discrimination training in adult owl monkeys. *J. of neuroscience*. 1993. 12: 87-103.
- Rosenbleuth, A, N Wiener, and J Bieglow. Behavior, purpose, and teleology. *Philosophy of science*. January 1943. 18-19.
- Sakurai, T, et al. Orexins and orexins receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. *Cell*. 1998. 92: 573-85.
- Salzman, CD, CM Murasugi, KH Britten, WT Newsome. Microstimulation of visual area MT: effects on direction discrimination performance. *J neuroscience*. 1992. 12: 2478-2492.
- Schwartz, JH. Consciousnesses and the neurobiology of twenty-first century. In *Principles of Neural Science*. 4<sup>th</sup> edition. ER Kandel et al. New York: McGraw-Hill. 2000.
- Sehgal, A, et al. Rhythmic expression of *timeless*: A basis for promoting circadian cycles in *period* gene autoregulation. *Science*. 1995. 270: 808-810.

- Seidman, JG. Screening of recombinant DNA libraries. *Current protocols in molecular biology*. New York: John Wiley and Sons, Inc. 2000.
- Smolensky, P. Computational models of minds. *A companion to the philosophy of mind*. Guttenplan (ed.). Oxford: Blackwell Publishers, Ltd. 1994.
- Sokoloff, L. *Metabolic probes of central nervous system in experimental animals and man*. Sauderland, MA: Sinauer. 1984.
- Sperry, R. Neurology and the mind-body problem. *American scientist*. 1952. 40: 291-312.
- Stapp, HP. *Mind and quantum mechanics*. Springer verlag. 1993.
- Stevens, SS. *Psychophysics*. New Brunswick: Transaction Books. 1975/1986.
- Todd, PK and KJ Mack. Sensory stimulation increases cortical expression of the Fragile X Mental Retardation Protein *in vivo*. *Molecular Brain Research*. 2000. 80: 17-25.
- Tootell, RBH, et al. Visual motion aftereffect in cortical area MT as revealed by fMRI. *Nature*. 1995, 575: 139-141.
- Waltzman, SB, NI Cohen & WH Shapiro. Use of multichannel cochlear implant in the congenitally and prelingually deaf population. *Laryngoscope*. 1992, 102: 395-399.
- Wilson, SP, et al. Antihyperalgesic effects of infection with preproenkephalin-encoding herpes virus. *PNAS, USA*. 1999. 96: 3211-3216.